Elanco

Increxxa™ (tulathromycin injection)

TECH SHEET

IT'S ALL ABOUT BALANCE.

CONTROL AND TREAT BRD WITH LASTING CONFIDENCE.

Balance BRD and your budget with Increxxa™ (tulathromycin injection), featuring tulathromycin, the macrolide antibiotic you can trust to help your cattle breathe easier by fighting bovine respiratory disease (BRD).

Used metaphylactically, tulathromycin helps decrease the negative effects of BRD, such as morbidity and retreatment, leading to more profits by avoiding return trips to the hospital pen and getting healthy cattle back to the feedbunk.[1]

The addition of Increxxa to the extensive Elanco cattle portfolio provides yet another way to help combat BRD and help optimize herd health, efficiency and profits. As with all Elanco products, you can breathe easier knowing Increxxa is held to the company's uncompromising standards for potency, uniformity and quality.

- **BREATHE EASIER.** Quickly targets the site of infection in the lungs for fast-acting performance where it's needed.*[2]
- **LONG LASTING.** Has a long half-life, giving cattle more time to bolster an effective defense against BRD.*[2]
- **EFFECTIVE CONTROL.** Rapidly circulates to the lungs to control BRD early in the disease process.*[2]

*Clinical relevance is unknown.

INCREXXA IS AVAILABLE IN THE FOLLOWING PACKAGE SIZES:

- 100 mL vial
- 250 mL vial
- 500 mL vial

GUIDELINES & LABEL DIRECTIONS

INDICATIONS: Beef: Treatment of BRD and control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis*. Treatment of infectious bovine keratoconjunctivitis associated with *Moraxella bovis*. Treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii*. Suckling calves, dairy calves and veal calves: Treatment of BRD associated with *Mannheimia haemolytica, Pasteurella multocida, Haemophilus somni* and *Mycoplasma bovis*.

IMPORTANT SAFETY INFORMATION (ISI): Not for human use. Keep out of reach of children. Do not use in animals previously found to be hypersensitive to the drug. Increxxa has a pre-slaughter withdrawal time of 18 days. Do not use in female dairy cattle 20 months of age or older.

ADMINISTRATION: In cattle, inject subcutaneously as a single dose in the neck at a dosage of 2.5 mg/kg (1.1 mL/100 lbs.) body weight. Do not inject more than 10 mL per injection site.

STORAGE: Store below 25 C (77 F) with excursions up to 40 C (104 F).

The label contains complete use information, including cautions and warnings. Always read, understand and follow the label and use directions.

FOR MORE INFORMATION ON INCREXXA, CONSULT YOUR ELANCO REPRESENTATIVE.

[1] Abell K, Theurer M, Larson R, et al. A mixed treatment comparison meta-analysis of metaphylaxis treatments for bovine respiratory disease in beef cattle. J Anim Sci. 2017. 95(2):626-35.
[2] Villarino N, Brown S, Martin-Jimenez T. Understanding the pharmacokinetics of tulathromycin: a pulmonary perspective. Vet Pharmacol Ther. 2014. 37(3):211-21.

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FULL PRESCRIBING INFORMATION FOR USE IN CATTLE ONLY
SEE PRODUCT INSERT FOR COMPLETE DOSING AND ADMINISTRATION INFORMATION

Elanco™ Increxxa™ (tulathromycin injection)

Injectable Solution

Antibiotic

100 mg of tulathromycin/mL

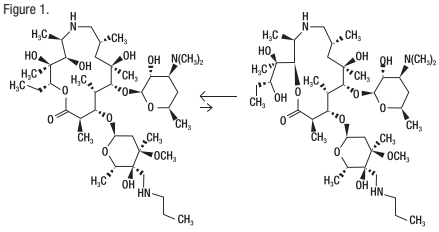
For use in beef cattle (including suckling calves), non-lactating dairy cattle (including dairy calves) and veal calves. Not for use in female dairy cattle 20 months of age or older.

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

Increxxa Injectable Solution is a ready-to-use sterile parenteral preparation containing tulathromycin, a semi-synthetic macrolide antibiotic of the subclass triamilide. Each mL of Increxxa contains 100 mg of tulathromycin, 500 mg propylene glycol, 19.2 mg citric acid and 5 mg monothioglycerol. Sodium hydroxide or hydrochloric acid may be added to adjust pH. Increxxa consists of an equilibrated mixture of two isomeric forms of tulathromycin in a 9:1 ratio. Structures of the isomers are shown below.

Figure 1.



The chemical names of the isomers are (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino) methyl]-a-L-ribo-hexopyranosyl] oxy]-2-ethyl-3,4,10- trihydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-ß-D-xylo-hexopyranosyl]-oxy]-1-oxa-6-azacyclopentadecan-15-one and (2R,3R,6R,8R,9R,10S,11S,12R)-11-[[2,6-dideoxy-3-C-methyl- 3-O-methyl-4-C-[(propylamino)methyl]-a-L-ribo-hexopyrano-syl]oxy]-2-[(1R,2R)-1,2-dihydroxy-1-methylbutyl]-8-hydroxy-3,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-ß-D-xylo-hexopyranosyl]oxy]-1-oxa-4-azacyclotridecan-13-one, respectively.

INDICATIONS

Beef and Non-Lactating Dairy Cattle

BRD – Increxxa Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni,* and *Mycoplasma bovis;* and for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni, and Mycoplasma bovis.*

IBK – Increxxa Injectable Solution is indicated for the treatment of infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis.*

Foot Rot – Increxxa Injectable Solution is indicated for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii.*

Suckling Calves, Dairy Calves, and Veal Calves

BRD – Increxxa Injectable Solution is indicated for the treatment of BRD associated with M. haemolytica, P. multocida, H. somni, and M. bovis.

DOSAGE AND ADMINISTRATION

Cattle

Inject subcutaneously as a single dose in the neck at a dosage of 2.5 mg/kg (1.1 mL/100 lb) body weight (BW). Do not inject more than 10 mL per injection site.

Table 1. Increxxa Cattle Dosing Guide

Animal Weight (Pounds)	Dose Volume (mL)
100	1.1
200	2.3
300	3.4
400	4.5
500	5.7
600	6.8
700	8.0
800	9.1
900	10.2
1000	11.4

CONTRAINDICATIONS

The use of Increxxa Injectable Solution is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS

FOR USE IN ANIMALS ONLY.

NOT FOR HUMAN USE.

KEEP OUT OF REACH OF CHILDREN.

NOT FOR USE IN CHICKENS OR TURKEYS.

RESIDUE WARNINGS

Cattle

Cattle intended for human consumption must not be slaughtered within 18 days from the last treatment. This drug is not approved for use in female dairy cattle 20 months of age or older, including dry dairy cows. Use in these cattle may cause drug residues in milk and/or in calves born to these cows.

PRECAUTIONS

Cattle

The effects of Increxxa on bovine reproductive performance, pregnancy, and lactation have not been determined. Subcutaneous injection can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.

ADVERSE REACTIONS

Cattle

In one BRD field study, two calves treated with tulathromycin injection at 2.5 mg/kg BW exhibited transient hypersalivation. One of these calves also exhibited transient dyspnea, which may have been related to pneumonia.

POST APPROVAL EXPERIENCE

The following adverse events are based on post approval adverse drug experience reporting. Not all adverse events are reported to the FDA CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The following adverse events are listed in decreasing order of reporting frequency in cattle: Injection site reactions and anaphylaxis/anaphylactoid reactions. For additional information about reporting adverse drug experiences for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

CLINICAL PHARMACOLOGY

At physiological pH, tulathromycin (a weak base) is approximately 50 times more soluble in hydrophilic than hydrophobic media. This solubility profile is consistent with the extracellular pathogen activity typically associated with the macrolides.1 Markedly higher tulathromycin concentrations are observed in the lungs as compared to the plasma. The extent to which lung concentrations represent free (active) drug was not examined. Therefore, the clinical relevance of these elevated lung concentrations is undetermined. Although the relationship between tulathromycin and the characteristics of its antimicrobial e ects has not been characterized, as a class, macrolides tend to be primarily bacteriostatic, but may be bactericidal against some pathogens. 2 They also tend to exhibit concentration independent killing; the rate of bacterial eradication does not change once serum drug concentrations reach 2 to 3 times the minimum inhibitory concentration (MIC) of the targeted pathogen. Under these conditions, the time that serum concentrations remain above the MIC becomes the major determinant of antimicrobial activity. Macrolides also exhibit a post-antibiotic e ect (PAE), the duration of which tends to be both drug and pathogen dependent. In general, by increasing the macrolide concentration and the exposure time, the PAE will increase to some maximal duration. Of the two variables, concentration and exposure time, drug concentration tends to be the most powerful determinant of the duration of PAE. Tulathromycin is eliminated from the body primarily unchanged via biliary excretion.

1 *Carbon, C. 1998. Pharmacodynamics of Macrolides, Azalides, and Streptogramins: Effect on Extracellular Pathogens. Clin. Infect. Dis., **27**:28-32.*

2 *Nightingale, C.J. 1997. Pharmacokinetics and Pharmacodynamics of Newer Macrolides. Pediatr. Infect. Dis. J., **16**:438-443.*

Cattle

Following subcutaneous administration into the neck of feeder calves at a dosage of 2.5 mg/kg BW, tulathromycin is rapidly and nearly completely absorbed. Peak plasma concentrations generally occur within 15 minutes after dosing and product relative bioavailability exceeds 90%. Total systemic clearance is approximately 170 mL/hr/kg. Tulathromycin distributes extensively into body tissues, as evidenced by volume of distribution values of approximately 11 L/kg in healthy ruminating calves. [3] This extensive volume of distribution is largely responsible for the long elimination half-life of this compound [approximately 2.75 days in the plasma (based on quantifiable terminal plasma drug concentrations) versus 8.75 days for total lung concentrations (based on data from healthy animals)]. Linear pharmacokinetics are observed with subcutaneous doses ranging from 1.27 mg/kg BW to 5.0 mg/kg BW. No pharmacokinetic differences are observed in castrated male versus female calves.

3 *Clearance and volume estimates are based on intersubject comparisons of 2.5 mg/kg BW administered by either subcutaneous or intravenous injection.*

MICROBIOLOGY

Cattle

Tulathromycin has demonstrated in vitro activity against *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni,* and *Mycoplasma bovis,* four pathogens associated with BRD; against *Moraxella bovis* associated with IBK; and against *Fusobacterium necrophorum* and *Porphyromonas levii* associated with bovine foot rot. The MICs of tulathromycin against indicated BRD and IBK pathogens were determined using methods recommended by the Clinical and Laboratory Standards Institute (CLSI, M31-A2). The MICs against foot rot pathogens were also determined using methods recommended by the CLSI (M11-A6). All MIC values were determined using the 9:1 isomer ratio of this compound.

BRD - The MICs of tulathromycin were determined for BRD isolates obtained from calves enrolled in therapeutic and at-risk field studies in the U.S. in 1999. In the therapeutic studies, isolates were obtained from pre-treatment nasopharyngeal swabs from all study calves, and from lung swabs or lung tissue of saline-treated calves that died. In the at-risk studies, isolates were obtained from nasopharyngeal swabs of saline-treated non-responders, and from lung swabs or lung tissue of saline-treated calves that died. The results are shown in Table 3.

IBK - The MICs of tulathromycin were determined for *Moraxella bovis* isolates obtained from calves enrolled in IBK field studies in the U.S. in 2004. Isolates were obtained from pre-treatment conjunctival swabs of calves with clinical signs of IBK enrolled in the tulathromycin injection and saline-treated groups. The results are shown in Table 3.

Foot Rot - The MICs of tulathromycin were determined for *Fusobacterium necrophorum* and *Porphyromonas levii* obtained from cattle enrolled in foot rot field studies in the U.S. and Canada in 2007. Isolates were obtained from pre-treatment interdigital biopsies and swabs of cattle with clinical signs of foot rot enrolled in the tulathromycin injection and saline-treated groups. The results are shown in Table 3.

Table 3. Tulathromycin minimum inhibitory concentration (MIC) values* for indicated pathogens isolated from field studies evaluating BRD and IBK in the U.S. and from foot rot field studies in the U.S. and Canada.

Indicated pathogen	Date isolated	No. of isolates	MIC_{50} ** (µg/mL)	MIC_{90} ** (µg/mL)	MIC range (µg/mL)
Mannheimia haemolytica	1999	642	2	2	0.5 to 64
Pasteurella multocida	1999	221	0.5	1	0.25 to 64
Histophilus somni	1999	36	4	4	1 to 4
Mycoplasma bovis	1999	43	0.125	1	≤ 0.063 to > 64
Moraxella bovis	2004	55	0.5	0.5	0.25 to 1
Fusobacterium necrophorum	2007	116	2	64	≤ 0.25 to > 128
Porphyromonas levii	2007	103	8	128	≤ 0.25 to > 128

* The correlation between *in vitro* susceptibility data and clinical e ectiveness is unknown.

** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

EFFECTIVENESS

Cattle

BRD – In a multi-location field study, 314 calves with naturally occurring BRD were treated with tulathromycin injection. Responses to treatment were compared to saline-treated controls. A cure was defined as a calf with normal attitude/activity, normal respiration, and a rectal temperature of ≤ 104°F on Day 14. The cure rate was significantly higher ($P \leq 0.05$) in tulathromycin injection-treated calves (78%) compared to saline-treated calves (24%). There were two BRD-related deaths in the tulathromycin injection-treated calves compared to nine BRD-related deaths in the saline-treated calves. Fifty-two tulathromycin injectiontreated calves and 27 saline-treated calves from the multi-location field BRD treatment study had *Mycoplasma bovis* identified in cultures from pre-treatment nasopharyngeal swabs. Of the 52 tulathromycin injection-treated calves, 37 (71.2%) calves were categorized as cures and 15 (28.8%) calves were categorized as treatment failures. Of the 27 salinetreated calves, 4 (14.8%) calves were categorized as cures and 23 (85.2%) calves were treatment failures.

A Bayesian meta-analysis was conducted to compare the BRD treatment success rate in young calves (calves weighing 250 lbs or less and fed primarily a milk-based diet) treated with tulathromycin injection to the success rate in older calves (calves weighing more than 250 lbs and fed primarily a roughage and grain-based diet) treated with tulathromycin injection. The analysis included data from four BRD treatment effectiveness studies conducted for the approval of tulathromycin injection in the U.S. and nine contemporaneous studies conducted in Europe. The analysis showed that the BRD treatment success rate in young calves was at least as good as the BRD treatment success rate in older calves. As a result, tulathromycin injection is considered effective for the treatment of BRD associated with *M. haemolytica, P. multocida, H. somni,* and *M. bovis* in suckling calves, dairy calves, and veal calves.

In another multi-location field study with 399 calves at high risk of developing BRD, administration of tulathromycin injection resulted in a significantly reduced incidence of BRD (11%) compared to saline-treated calves (59%). Effectiveness evaluation was based on scored clinical signs of normal attitude/activity, normal respiration, and a rectal temperature of ≤ 104°F on Day 14. There were no BRD-related deaths in the tulathromycin injectiontreated calves compared to two BRD-related deaths in the saline-treated calves.

Fifty saline-treated calves classified as non-responders in this study had *Mycoplasma bovis* identified in cultures of post-treatment nasopharyngeal swabs or lung tissue.

Two induced infection model studies were conducted to confirm the e ectiveness of tulathromycin injection against *Mycoplasma bovis.* A total of 166 calves were inoculated intratracheally with field strains of *Mycoplasma bovis.* When calves became pyrexic and had abnormal respiration scores, they were treated with either tulathromycin injection (2.5 mg/kg BW) subcutaneously or an equivalent volume of saline. Calves were observed for signs of BRD for 14 days post-treatment, then were euthanized and necropsied. In both studies, mean lung lesion percentages were statistically significantly lower in the tulathromycin injection-treated calves compared with saline-treated calves (11.3% vs. 28.9%, $P = 0.0001$ and 15.0% vs. 30.7%, $P < 0.0001$).

IBK – Two field studies were conducted evaluating tulathromycin injection for the treatment of IBK associated with *Moraxella bovis* in 200 naturally-infected calves. The primary clinical endpoint of these studies was cure rate, defined as a calf with no clinical signs of IBK and no corneal ulcer, assessed on Days 5, 9, 13, 17, and 21. Time to improvement, defined as the first day on which a calf had no clinical signs of IBK in both eyes, provided that those scores were maintained at the next day of observation, was assessed as a secondary variable. At all time points, in both studies, the cure rate was significantly higher ($P < 0.05$) for tulathromycin injection-treated calves compared to saline-treated calves. Additionally, time to improvement was significantly less ($P < 0.0001$) in both studies for tulathromycin injection-treated calves compared to saline-treated calves.

Foot Rot - The effectiveness of tulathromycin injection for the treatment of bovine foot rot was evaluated in 170 cattle in two field studies. Cattle diagnosed with bovine foot rot were enrolled and treated with a single subcutaneous dose of tulathromycin injection (2.5 mg/kg BW) or an equivalent volume of saline. Cattle were clinically evaluated 7 days after treatment for treatment success, which was based on defined decreases in lesion, swelling, and lameness scores. In both studies, the treatment success percentage was statistically significantly higher in tulathromycin injection-treated calves compared with saline-treated calves (60% vs. 8%, $P < 0.0001$ and 83.3% vs. 50%, $P = 0.0088$).

ANIMAL SAFETY

Cattle

Safety studies were conducted in feeder calves receiving a single subcutaneous dose of 25 mg/kg BW, or 3 weekly subcutaneous doses of 2.5, 7.5, or 12.5 mg/kg BW. In all groups, transient indications of pain after injection were seen, including head shaking and pawing at the ground. Injection site swelling, discoloration of the subcutaneous tissues at the injection site and corresponding histopathologic changes were seen in animals in all dosage groups. These lesions showed signs of resolving over time. No other drug-related lesions were observed macroscopically or microscopically. An exploratory study was conducted in feeder calves receiving a single subcutaneous dose of 10, 12.5, or 15 mg/kg BW. Macroscopically, no lesions were observed. Microscopically, minimal to mild myocardial degeneration was seen in one of six calves administered 12.5 mg/kg BW and two of six calves administered 15 mg/kg BW.

A safety study was conducted in preruminant calves 13 to 27 days of age receiving 2.5 mg/kg BW or 7.5 mg/kg BW once subcutaneously. With the exception of minimal to mild injection site reactions, no drug-related clinical signs or other lesions were observed macroscopically or microscopically.

STORAGE CONDITIONS

Store below 25°C (77°F), with excursions up to 40°C (104°F).

100 mL: Use within 2 months of first puncture and puncture a maximum of 67 times. If more than 67 punctures are anticipated, the use of multi-dosing equipment is recommended. When using a draw-off spike or needle with bore diameter larger than 16 gauge, discard any product remaining in the vial immediately after use.

250 mL: Use within 2 months of first puncture and puncture a maximum of 100 times. If more than 100 punctures are anticipated, the use of multi-dosing equipment is recommended. When using a draw-off spike or needle with bore diameter larger than 16 gauge, discard any product remaining in the vial immediately after use.

HOW SUPPLIED

Increxxa (tulathromycin injection) Injectable Solution is available in the following package sizes:
100 mL vial
250 mL vial
500 mL vial

For product questions, to report adverse reactions, or for a copy of the Safety Data Sheet (SDS), call Elanco Product & Veterinary Support at 1-800-428-4441. For additional information about reporting adverse drug experiences for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

Approved by FDA under ANADA # 200-666

Product of China.

Manufactured for: Elanco US Inc., Greenfield, IN 46140 U.S.A.

TAKE TIME

OBSERVE LABEL DIRECTIONS

Elanco™